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ABSTRACT (word count 200)

Aims: to test safety of new buprenorphine oral lyophilisate wafer ('bup-lyo') versus standard sub-lingual buprenorphine ('bup-SL').

Design: randomised (2:1) open-label study; opioid-dependent subjects; subsequent partial cross-over.

Settings: specialised clinical trials facility and addictions treatment facility.

Participants: opioid-dependent subjects (n=36) commencing buprenorphine maintenance (personalized dose-titration) including patients co-using alcohol, cocaine, benzodiazepines (below thresholds).

Measurements: respiratory function (respiratory rate, pulse-oximetry); medication hold and dose adequacy; opiate withdrawal signs and symptoms; tablet disintegration times; treatment retention. Pharmacokinetics for plasma buprenorphine and norbuprenorphine (n=11).

Findings: Oral lyophilized buprenorphine ('bup-lyo') completely dissolved within 2 mins for 58% versus 5% for 'bup-SL'. Dose titration resulted in similar maintenance dosing (10.8mg versus 9.6mg). No significant between-group differences in opiate withdrawal phenomena, craving, adequacy of 'hold', respiratory function. No serious adverse events (SAEs), nor 'severe' adverse events (AEs), although more AEs and Treatment-Emergent Adverse Events (TEAEs) with 'bup-lyo' (mostly 'mild'). Pharmacokinetics greater bioavailability of buprenorphine with 'bup-lyo' (but not norbuprenorphine).

Conclusions: Orally-disintegrating buprenorphine oral lyophilisate wafer disintegrated rapidly. No increased respiratory depression was found and clinically no difference between medications was observed. Pharmacokinetics found substantially increased bioavailability of buprenorphine (but not of nor-buprenorphine) with 'bup-lyo' relative to 'bup-SL'. In supervised dosing contexts, rapidly-disintegrating formulations may enable wider buprenorphine prescribing.

Key words: opiate addiction; buprenorphine; new treatment; lyophilised; safety study; randomised trial; rapidly-disintegrating buprenorphine, opioid substitute therapy, phase II trial

BACKGROUND

Buprenorphine is a partial mu-agonist approved for maintenance treatment of heroin/opiate addiction. Sublingual formulations of buprenorphine have been extensively introduced in many countries over the last 20 years. Studies have consistently found that buprenorphine maintenance reduces heroin/opiate use, reduces injecting and reduces deaths [1–5]. Buprenorphine is also used for detoxification [6].

Current treatments still fail many patients, with approximately 50% of patients dropping out of both buprenorphine and methadone maintenance treatment within 6 months [7]. Failure of opioid substitution treatment (OST) derives partly from poor/non-adherence and diversion of supplies. Supervised dosing is often recommended [8], but is difficult since standard sublingual buprenorphine can take 5-10 mins to dissolve. Extended supervision is also impractical in some situations e.g. busy community pharmacies; treatment in prison. Rapidly-dissolving or rapid-dispersal formulations, such as the combination buprenorphine/naloxone film [9,10] available in some parts of the world and the lyophilised tablet (described below), may be beneficial in busy community pharmacies and custodial settings and enable wider prescribing of buprenorphine in community and custodial settings.

A further characteristic of buprenorphine is the reported much lower respiratory depressant effect. A ceiling effect for respiratory depression with buprenorphine has been described [11–13] with respiratory rate broadly stable across doses [14].

We report results from a ‘first-in-patient’ safety trial of a new buprenorphine oral lyophilisate (mono-product) formulation relative to standard sublingual buprenorphine, including scrutiny for any associated respiratory depression; plus bio-availability data on a consenting subset.

METHOD

Study Design and randomisation:

A randomised, open-label study was conducted, investigating safety of a new buprenorphine oral lyophilisate wafer (based on Zydys technology [15,16] compared to standard sub-lingual buprenorphine tablets, covering dose induction and maintenance in opioid-dependent subjects (See Figure 1). The study was approved by Brent, London, UK Ethical committee and registered with EudraCT Number: 2012-003560-49. Subjects were randomised (2:1 ratio) to receive buprenorphine as either the novel buprenorphine oral lyophilisate (approved by regulatory authorities in the UK, Sweden and Malta as 'Espranor', hereafter 'bup-lyo')(n=23) or standard sub-lingual buprenorphine ('Subutex', hereafter 'bup-SL')(n=13), with stratification for regular benzodiazepine use. Sample size was selected after discussion with the UK regulatory authority. Treatment comprised a Dose Titration Period (Days 1-7), Maintenance Period (Days 8-14), then an Extension Period (Days 15-29) during which 'bup-lyo' subjects were switched to 'bup-SL' for ongoing treatment.

Venous cannulation and collection of blood samples for pharmacokinetic study was undertaken with a consenting sub-set of study subjects on Day 1 of Titration period, Days 2 and 7 of Maintenance period, and last day of Extension period.

***** Insert Figure 1 (flow diagram and numbers) about here *****

Subjects/Patients:

The study cohort comprised 36 opiate-dependent subjects commencing opiate substitution/maintenance treatment with buprenorphine. Eleven subjects consented to, and had adequate venous access for insertion of indwelling cannula for the supplementary pharmacokinetic study.

Diagnosis and Inclusion/Exclusion Criteria:

All subjects were diagnosed opiate-dependent as per DSM-IV-TR criteria (see Table 1), and were awaiting buprenorphine maintenance treatment (either as new patient, or as scheduled change of treatment). The other inclusion/exclusion criteria (Table 1) deliberately allowed inclusion of subjects with a degree of concurrent use of other drugs (alcohol, cannabis, cocaine) provided this did not constitute the primary diagnosis and did not have a severity that compromised participation in the trial. Similarly, in order to increase real-world applicability and improve generalisability, patients with co-existing physical and mental health disorders (e.g. chronic liver disease, depression) were included, provided severity was not likely to compromise ability to participate in the trial (see web-appendix Table A1).

If subjects had taken either buprenorphine or methadone within one day of the scheduled commencement of study treatment, they could enter a pre-randomisation loop, during which buprenorphine and methadone were excluded for at least one day and subjects provided with oral morphine if necessary (and then re-considered for the study).

Study medications and their dose titration:

The novel experimental formulation: 'bup-lyo' wafer (buprenorphine oral lyophilisate, for which we used 'Espranor', registered in 2015 in UK, Sweden and Malta) was administered oro-mucosally (on the tongue), as a freeze-dried, rapidly-dispersing wafer form with porous air-filled structure, for administration without water, and disintegrating rapidly on contact with moisture [15]. Zydys formulations are specifically designed for rapid dispersion on the tongue, as with other orally disintegrating tablets [16].

The reference formulation: 'bup-SL' tablet (standard sub-lingual buprenorphine, for which we used the commercial product 'Subutex') was administered sublingually with instruction to be retained until disintegration (as per manufacturers' instructions and regular clinical practice).

Dose titration and Treatment during the study period:

During the initial Dose Titration Period (Days 1-7), buprenorphine dose was an initial 2-4mg on the first day with an additional 2-4mg if clinically required, then increased daily, according to clinical response, up to maximum dose of 24mg/day ('bup-lyo') or 32mg/day ('bup-SL'). During the 7-day Maintenance Period, dosing was fixed.

Clinical procedures are described in Table 1.

*** Insert Table 1 about here ***

Measures:

Retention in treatment was measured as the proportion remaining in treatment at (a) end of titration, and (b) end of the maintenance period.

Medication 'hold' and dose adequacy were measured with Likert scales. Opiate withdrawal signs and symptoms were measured using previously validated scales (Objective Opiate Withdrawal Scale (OOWS) and Subjective Opiate Withdrawal Scale (SOWS)) [17].

Oral disintegration time of 'bup-lyo' and 'bup-SL' were measured by direct observation, measuring (a) time to disintegration (i.e. tablet could no longer be removed intact) and (b) time until completely dissolved.

Ongoing monitoring included respiratory rate, pulse-oximetry, urine drug screens, plus routine safety assessments including pre/post liver function tests, ECG, pregnancy test.

Pulse-oximetry was monitored continuously for up to 3 hours post-dose during each Titration Day (until stable dose) and Days 2 and 7 of Maintenance Period. Subjective (Likert and SOWS) and objective assessments (OOWS) were performed pre-dosing.

Supplementary study of pharmacokinetics:

Eleven subjects consented to, and had adequate venous access for, cannulation to provide blood samples. These were collected at 0, 5, 10, 15, 30, 60, 120 and 180 mins on Day 1 of the Titration Period and Days 2 and 7 of the Maintenance Period, and the last day of the Extension Period.

Buprenorphine and also the active metabolite norbuprenorphine were assayed by LC-MS-MS (Liquid Chromatography Tandem Mass Spectrometry, Simbec Research Ltd. Merthyr Tydfil, UK), since animal studies identify norbuprenorphine as a potent respiratory depressant [18–21].

Statistical Methods:

The study sample for analysis was all subjects who received at least one dose of study medication: 23 subjects 'bup-lyo', 13 subjects 'bup-SL'.

To allow for potential differences in treatment group baselines, the two treatments during the Maintenance phase (Day 2 and Day 7) was compared utilising the change in Likert, SOWS and OOWS scores from baseline (end titration). Similarly, the respiratory safety of the two treatments during the Maintenance phase was also compared changes in oximetry records from baseline (end titration). These safety assessments included incidents of SpO₂% saturation <90% of ≥1 min and total duration of SpO₂% saturation <90% over 0-30 mins and 0-120 mins post-dose. Respiratory safety end points were statistically compared by Wilcoxon Rank Sum test. Respiratory rates pre-dose and 15, 30, and 60 mins post-dose were statistically compared by (ANOVA). All tests were performed with Statistical Analysis System (SAS) V9.3 (SAS Institute Inc., Cary, NC, USA).

Subjects randomised to 'bup-lyo' were switched on Day 15 to 'bup-SL'. It was thus possible also to compare the two products within-subject; this will be reported separately.

Pharmacokinetics:

Buprenorphine and norbuprenorphine C_{\max} , T_{\max} , and AUC_{0-3hr} were determined separately for buprenorphine and norbuprenorphine utilising Phoenix® WinNonlin® V6.3 software (Pharsight, Princeton, NJ, USA). Data were examined by treatment group and dose at each of the four PK sampling periods.

RESULTS

Fifty-five subjects were screened, of whom 17 subjects (30.9%) did not meet inclusion/exclusion criteria (Figure 1). Two randomised subjects did not receive study treatment (one withdrawing consent, one lost contact). A total of 36 subjects received treatment and comprised the study population; 23 randomised to 'bup-lyo', 13 to 'bup-SL'. Two subjects (one in each group) were regular benzodiazepine users.

Eleven subjects also participated in the PK study (8 'bup-lyo'; 3 'bup-SL'). Two subjects (one per group) withdrew during the Extension Period, and cannulae blockage spoilt PK on a further two ('bup-lyo') at final (Extension) assessment.

Demographics and drug use histories:

The study sample were typical of people presenting for treatment of opiate dependence, although slightly older (mean \pm SD, 42 ± 8.6 , range 23-58 years), mostly white Caucasian (64%) and with a higher proportion male (86%). Age of first opiate use was 25 ± 8.8 , range 11-42 years); duration of heroin/opiate use prior to the study was 17 ± 11 , range 3-47 years); 50% (18) had ever injected (3 currently) (fuller detail in Table 2).

***** Insert Table 2 (demographics and drug use) about here *****

Retention and attrition through titration and maintenance periods:

Retention across the 28-day study was 87% (20/23) in 'bup-lyo' and 77% (10/13) in 'bup-SL' (difference not statistically significant). Retention during the first 14 days (when subjects were randomised to medication) was 96% for 'bup-lyo' versus 85% for 'bup-SL' at end of Titration, and 91% and 85% respectively at end of Maintenance (differences not statistically significant)(see web-appendix Figure A1). Thirty (83.3%) completed the entire 28 days.

Intensity of withdrawal symptoms, craving, and adequacy of 'hold':

For both medications, moderately high levels of withdrawal severity on Day 1 were evident (OOWS and SOWS), then reducing rapidly to low levels within a couple of days, remaining low throughout the remainder of the study period. No significant between-group differences were detected. See web-appendix Figures A2a&b for OOWS and SOWS over time, and A3a-c for intensity of withdrawal, intensity of craving and of adequacy of medication 'hold'.

The Titration Period:

Daily doses were individually tailored to clinical response. For 'bup-lyo' subjects (n=22/23 successfully titrated), mean \pm SD maintenance daily dose was 10.8 ± 4.9 mg, with three (14%) on ≤ 4 mg, six (27%) on 6-8mg, nine (41%) on 10-14mg, three (14%) on 16mg, and one (5%) on 20mg. For 'bup-SL' subjects (n=11/13 successfully titrated), mean maintenance daily dose was 9.6 ± 4.3 mg, with one subject (9%) on 4mg, seven (64%) on 6-8mg, and three (27%) on 16mg.

For both groups, the Titration period proceeded smoothly with 18 'bup-lyo' subjects (81.8%) and 10 'bup-SL' subjects (90.9%) reaching their maintenance daily dose by Day 3 – see web-appendix Figure A4.

The Maintenance Period:

There were no statistically significant differences between 'bup-lyo' and 'bup-SL' in within-subject changes of either SOWS or OOWS scores from Baseline (Titration Day 7) to either Maintenance Days 2 or 7, nor with adequacy of 'hold', intensity of withdrawal, or intensity of craving.

Crossover: Dose changes required on switch from 'bup-lyo' to 'bup-SL':

No dose adjustment was deemed clinically indicated for any of the 20 subjects on 'bup-lyo' who switched from 'bup-lyo' to 'bup-SL' at Day 15 (same prescribed dose), and there were no significant differences in subjective and objective scores.

Respiratory safety and respiratory function:

There was no statistically significant difference in respiratory depression between 'bup-lyo' and 'bup-SL' when comparing subject differences from Baseline (up to last valid Titration oximeter record) to Maintenance Days 2 and 7 for the number of SpO₂<90% events lasting ≥ 1 min or for the cumulative duration of SpO₂<90% in either the 0-30 min or 0-120 min post-dose period. There was also no statistically significant difference in respiratory depression between 'bup-lyo' and 'bup-SL' as determined by the difference in the mean number of SpO₂<90% events lasting ≥ 1 min in the 0-30 mins post-dose period at either Maintenance Days 2 or 7 ($p=0.20$ and 0.19 , respectively) from Baseline.

Similarly, there was no statistically significant difference between 'bup-lyo' and 'bup-SL' in the mean difference in total duration of SpO₂<90% ($p=0.87$ and 0.61 , respectively) during this period. Mean \pm SD durations of SpO₂<90% in the 0-30 mins post-dose period on Maintenance Days 2 and 7 were 6.1 ± 11.95 secs and 7.1 ± 13.47 secs in the 'bup-lyo' group compared to 177.0 ± 544.00 secs and 14.0 ± 31.25 secs in the 'bup-SL' group, respectively.

The same conclusions applied to the 0-120 min post-dose period assessments where no statistically significant differences between 'bup-lyo' and 'bup-SL' were observed for the mean difference in the number of SpO₂<90% events lasting ≥ 1 min at either Maintenance Days 2 or 7 (p = 0.18 and 0.19 respectively) and the mean difference in total duration of SpO₂<90% (p = 0.81 and 0.29, respectively). Mean ±SD durations of SpO₂<90% in the 0-120 mins post-dose period on Maintenance Days 2 and 7 were 68.0 ± 92.37 secs and 61.1 ± 88.94 secs in the 'bup-lyo' group compared to 499.3 ± 959.26 secs and 226.0 ± 281.46 secs in the 'bup-SL' group. There were no statistically significant differences between 'bup-lyo' and 'bup-SL' for either the mean respiration rate or mean categorical SpO₂% during the 0-60 mins post-dose periods across assessment sessions. Numerical values are summarised in Table 3, and graphically displayed in Figures A5a&b (Web-Appendix).

*** Insert Table 3 about here ***

Adverse Events:

There were no deaths and no Serious Adverse Events (SAE).

No Adverse Event (AE) was scored 'severe'. No Treatment-Emergent Adverse Events (TEAE) resulted in withdrawal. However, a greater proportion of 'bup-lyo' subjects experienced at least one AE and similarly for TEAE (73.9% and 69.6% respectively) compared to the 'bup-SL' group (30.8% and 15.4%, respectively). These mostly scored 'mild', with similar proportions of 'moderate' AEs in both treatment groups ('bup-lyo'=17.4%, 'bup-SL'=23.1%) (see [Web-Appendix Table A2](#)). Moderate TEAEs reported by ≥2 subjects included vomiting, arthralgia, hyperhidrosis, and nausea. However, more 'bup-lyo' subjects reported a greater number of 'mild' TEAEs (48 TEAEs in 17 subjects, 73.9%) versus 'bup-SL' subjects (9 TEAEs in 4 subjects, 30.8%). All of these 'mild' TEAEs were self-limiting.

The most frequently reported TEAE was headache in the 'bup-lyo' group (4 subjects, 17.4%). There were three events of oral hypoaesthesia from two 'bup-lyo' subjects at 5 and 10 mins post-administration; these resolved within 20 mins, 20 to 25 mins, and 'within an hour'. One subject also experienced an intermittent itchy feeling at the back of the throat (pruritus). All these events were considered mild but possibly related to study medication.

Laboratory test results, physical examination, and ECG recordings:

No clinically significant differences were observed between groups, with findings consistent with expectations for this patient population.

The majority of subjects in both treatment groups had at least one positive report from drug testing for cocaine ('bup-lyo'=52.2%, 'bup-SL' = 76.9%) during Titration and/or Maintenance.

*** Insert Figure 2 about here – time to disintegration ***

Disintegration and solubility of the 'bup-lyo' and 'bup-SL' tablets:

At dosing occasions, a record was made of both time to disintegration (i.e. tablet could no longer be removed intact) and time to completely dissolved. Over all periods, 96.3% of 'bup-lyo' administrations achieved partial disintegration on the tongue in ≤ 15 secs, versus 71.8% with 'bup-SL' ($p < 0.001$). At 2 mins, 'bup-lyo' had completely dissolved in 58.0% of administrations versus only 5.1% ('bup-SL') ($p < 0.0001$). The median time for tablets to completely dissolve was 2.0 mins for 'bup-lyo' versus 10 mins for 'bup-SL' ($p < 0.0001$).

All assessments of buccal mucosa during administration were reported as normal.

Pharmacokinetics (from volunteer sub-sample) - buprenorphine and nor-buprenorphine:

Analysable blood samples for pharmacokinetic (PK) were available from eleven subjects (8 'bup-lyo' and 3 'bup-SL'), yielding 21 sessions over Days 2 and 7 of the Maintenance Period (15 'bup-lyo', 6 'bup-SL').

Since subjects were on individualised maintenance doses, we examined PK curves for a dose-adjusted 4mg dose. Samples were collected on Days 2 and 7 of the Maintenance period (see Figure 3). In summary, these dose-normalised data find comparability in norbuprenorphine PK profiles between 'bup-lyo' and 'bup-SL' despite apparent increased bioavailability for 'bup-lyo' for buprenorphine concentrations.

*** insert Figure 3a&b about here – PK for buprenorphine and nor-buprenorphine ***

Of particular PK interest were the 5 subjects for which PK data were available following administration of both bup-Lyo and bup-SL. These subjects received the same dose of bup-Lyo on Maintenance Day 7 as bup-SL at Extension End (all had received repeat dosing for 13 to 15 days) and provide within subject relative bioavailability. For these subjects bup-Lyo demonstrated a higher mean [SD] buprenorphine bioavailability (Cmax: 185.8% [88.2] and AUC0-3 hr: 169.8% [62.0]) relative to bup-SL. However, for norbuprenorphine the mean [SD] bioavailability was comparable (Cmax: 109.6% [42.2] and AUC0-3 hr: 105.0% [39.4]) relative to bup-SL.

DISCUSSION

Very few clinical problems were encountered with the new buprenorphine oral lyophilisate wafer. The investigation only examined the early stages of treatment and the outpatient study was coordinated from a structured research facility: nevertheless, from a clinical standpoint, its use was found to be very similar to use of the standard sublingual buprenorphine during both induction or maintenance, with personalised maintenance dose achieved within three days for most patients, and equal retention rates across the two groups. Very similar scores were obtained on measures of adequacy of drug effect and with scores of withdrawal severity and craving. Furthermore, from the point of view of clinical management (and despite increased bioavailability subsequently identified), no dosage adjustment was necessary on switch-over from 'bup-lyo' to 'bup-SL'.

There was remarkably rapid disintegration of the lyophilisate tablets ('bup-lyo'), with complete disintegration by 3 mins for more than 75% of 'bup-lyo' administrations versus less than 25% of 'bup-SL' administrations. A serendipitous clinical observation was that, during dosing on the first days, some anxious patients had very dry mouths resulting in slower disintegration. This rapid disintegration and consequent greater ease of supervised dosing may increase feasibility of buprenorphine treatment in busy community and custodial settings when supervised dosing is still considered important. This now needs to be explored clinically.

No serious adverse events occurred, although there was higher reporting of (not serious) adverse events. Higher buprenorphine plasma levels with 'bup-lyo' might have contributed to this greater reporting rate although so too might open-label randomisation to a novel buprenorphine formulation. The active medication is the same in both formulations and thus this seems the likely explanation, although further study and pharmacovigilance are recommended.

A key purpose of the study was to investigate safety and, in particular, whether the increased bioavailability (observed by the manufacturer from prior healthy volunteer study, unpublished) might create any excess respiratory depressant effect. Across the trial, indices of respiratory depression remained minimal for both medications (continuous SpO₂ readings from finger pulse-oximetry, plus observation of respiratory rate), with no significant differences observed between the two medications on direct comparison. We are also conducting further exploratory analyses of the relationships between indices of respiratory depression and plasma levels of buprenorphine and nor-buprenorphine (on which we will report later).

The findings from the subsidiary pharmacokinetic study are interesting, although the small sample size means that the investigation needs confirmation with proper powered sample size. The good availability

of buprenorphine with the new lyophilised buprenorphine ('bup-lyo') means that, compared with 'bup-SL', there is substantial overall increased bioavailability of buprenorphine. Duration of action was similar. The low bio-availability of buprenorphine in 'bup-SL' has been reported previously, with approximately half the bioavailability when compared with the original buprenorphine liquid [22,23]. The combination buprenorphine/naloxone tablets ('Suboxone') was found to have 20% increased bioavailability versus 'bup-SL' [24], and a new generic buprenorphine/naloxone had approximately 40% increased bioavailability to Suboxone [25] (hence presumably even more bioavailable versus 'bup-SL'). Furthermore, some countries have a large proportion of patients receiving buprenorphine doses below recommended maintenance doses [26]: will the introduction of a formulation with better bio-availability result in either lower dose or alternatively higher effective dosing?

This increased bioavailability will presumably have implications for drug dosing. In regular clinical practice, dose titration is personalised and subsequent dose adjustments are based on individualised assessment of patient response. However, if there were need to switch patients between formulations, there would need to be guidance on dose adjustments to achieve equivalent effective dose. It is unclear how much this matters since, in this study, no clinical need to increase dose was identified when switching from 'bup-lyo' to 'bup-SL'.

In their Cochrane review, Mattick and colleagues [1] raise the possibility that the different drug effect from buprenorphine (compared with methadone) may account, at least in part, for the repeatedly observed lower retention rates with buprenorphine (versus methadone) [2–5,7]. There is a possibility, to be explored in future clinical trials, that the more rapid absorption of the new generation of tablets and wafers might produce an earlier perceived drug effect and, potentially, better retention rates with the new formulations of buprenorphine.

We find no increased bioavailability (in fact slightly lower plasma levels) of the metabolite norbuprenorphine, despite the increased bioavailability of buprenorphine itself. This is potentially interesting as norbuprenorphine is a more potent respiratory depressant (compared with buprenorphine itself). Indeed buprenorphine is, in animal studies at least, actually protective against the respiratory depressant effect of norbuprenorphine [27]. Might high plasma buprenorphine levels in conjunction with low norbuprenorphine levels be the desired relationship? We are conducting separate exploratory analyses of this aspect.

Limitations of the study need consideration. Although randomised, the study was open-label, and hence there is potential for bias in either direction – either concern about the new formulation, or alternatively a belief of greater effect. The study was modest sample size and also used a standard between-subject design and hence subjects were not identical. (We subsequently switched 'bup-lyo' patients back to

standard sublingual buprenorphine for continued treatment outside the trial on which we will report separately). Pharmacokinetic analyses were on very small sample size and pharmacokinetic data needed to be dose-normalised to enable meaningful comparison because each patient was dose-titrated to a personalised maintenance dose.

Two final considerations. The 'bup-lyo' lyophilised tablet is a mono-product. This is in sharp contrast to the combination buprenorphine/naloxone tablets more recently developed. Does it matter that it is without naloxone? For supervised dosing, there is no benefit from the inclusion of naloxone (if the supervised medication cannot be removed and concealed) although for unsupervised dosing the situation will require separate consideration.

Finally, is the development of a new 'rapidly disintegrating' oral formulation of buprenorphine worth the effort? It would seem successfully to address the major concern of concealment and later abuse associated with forms of buprenorphine with slow disintegration – this advantage would be expected to be similar for other recent rapid-dispersal buprenorphine formulations [28] Hopefully these rapid-dissolving variants of buprenorphine may increase the range of settings in which buprenorphine maintenance can safely be delivered, such as settings where it is unrealistic to expect full supervision of dosing over several minutes, e.g. busy community pharmacies and, especially, OST in the prison context (where average time per patient dosing is less than a minute per patient). These will be contexts which warrant particular attention in future studies.

Declaration of interests: We declare the following interests. JS is a researcher and clinician and has worked with a range of types of treatment and rehabilitation service-providers. He has contributed to the work of various governmental and non-governmental organisations and has received project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence), and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has also worked with pharmaceutical companies to seek to identify new or improved treatments (including, last 3 years, Martindale, Reckitt-Benckiser, MundiPharma, Rusan/iGen, Braeburn/MedPace) from whom he and his employer (King's College London) have received honoraria, travel costs, consultancy payments or trial medications. Funding received from Martindale Pharma includes funding to the King's Health Partners Clinical Trials Office for conduct of this study and also payment to his university employer for retained consultant status for JS's contribution to this work. JS's employer (King's College London) has registered intellectual property on a novel buccal naloxone (with which JS is involved), and JS has also been named in a patent registration by a Pharma company (declared above) as inventor of a potential concentrated naloxone nasal formulation (neither of these are directly connected to the study reported). Fuller detail of JS's interests is given at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>. JB has held consultancy agreements with Reckitt-Benckiser, Britannia pharmaceuticals and Martindale Pharma, and is PI on research grants funded by Reckitt-Benckiser and Martindale Pharma. SB is Medical Director of Martindale Pharma who have developed the study medication ('bup-lyo') and AK is employed by Martindale Pharma for specialist statistical advice on conduct and analyses of the study data.

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TABLES AND FIGURES

Table 1: Clinical procedures

Table 2: Characteristics of the two randomised groups ('bup-lyo' vs 'bup-SL') (total population in italics)

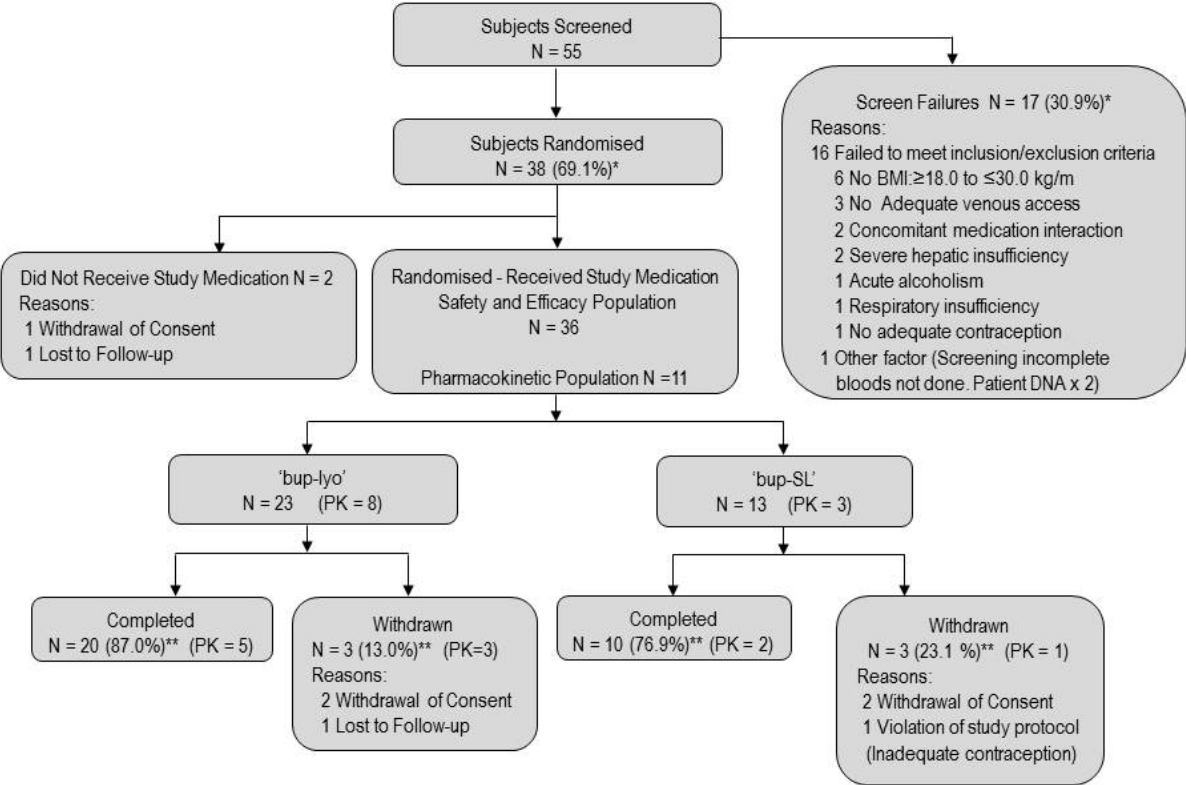
Table 3 - Assessments of respiratory function with continuous oximetry – 'bup-lyo' vs 'bup-SL'

Figure 1: Flow Diagram of the Study

Figure 2: Time to complete disintegration of tablets ('bup-lyo' vs 'bup-SL')

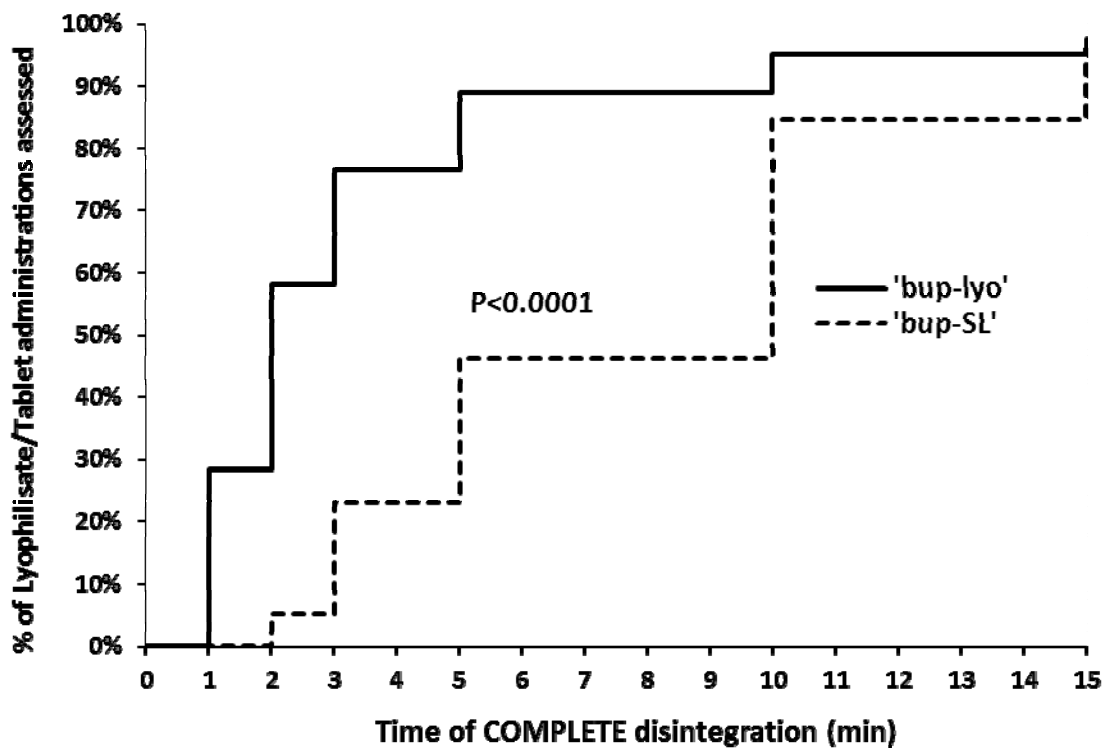
Figure 3a and b: (a) Mean (+SD) blood concentration-time profiles for (a) buprenorphine and (b) nor-buprenorphine (both figures dose-normalised to 4mg dose to allow analysis of patients on different personal maintenance doses)

Figure 2: Flow Diagram of the Study



*% Screened, **% 'bup-lyo' or 'bup-SL' administered study drug, PK = Pharmacokinetic study population, DNA = Did Not Attend

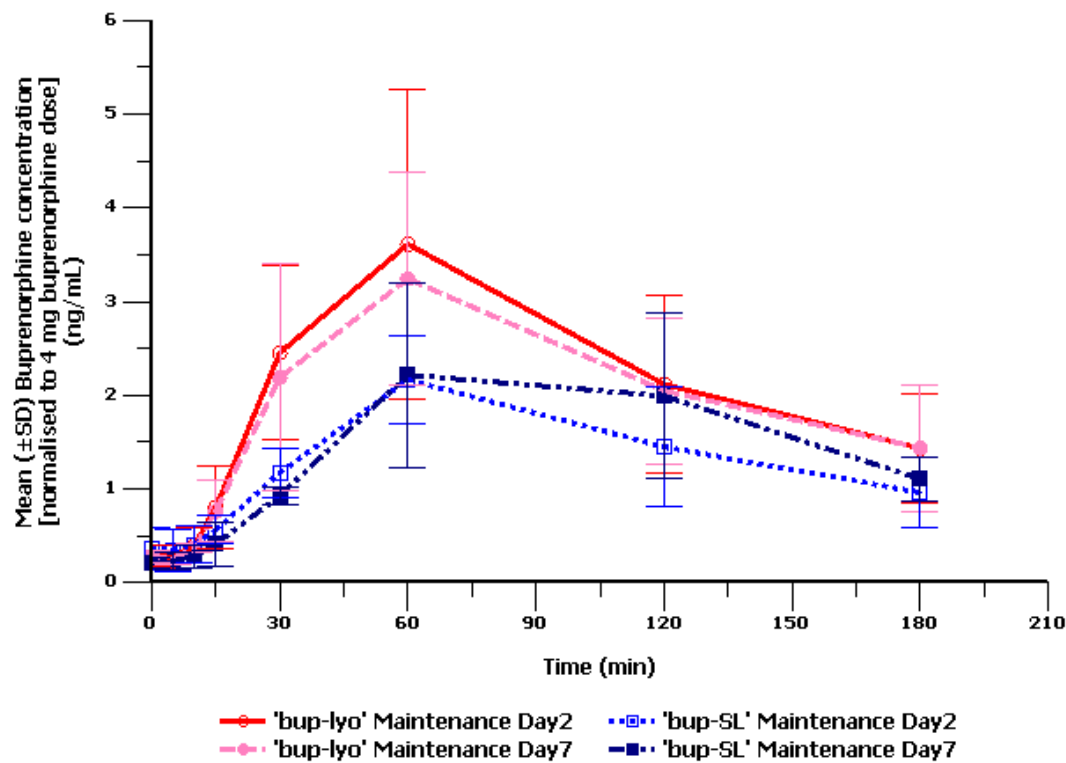
Figure 2: Time to complete disintegration of tablets ('bup-lyo' vs 'bup-SL')



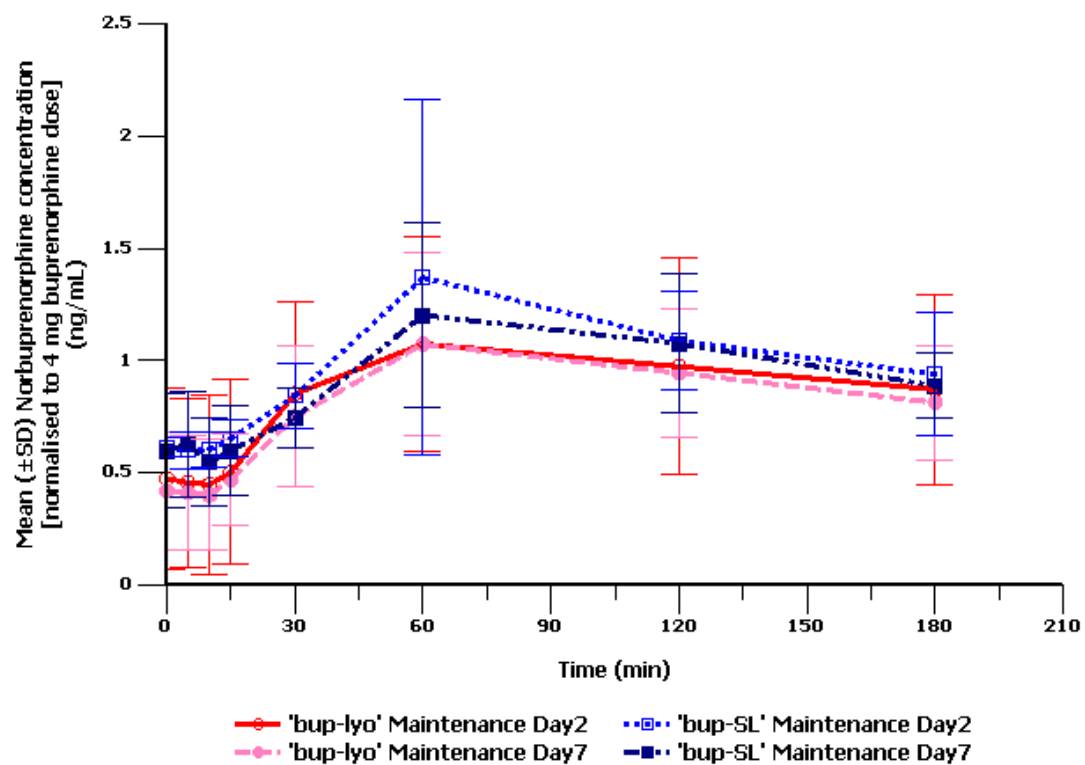
Median time to Complete Disintegration	'bup-lyo'	'bup-SL'
Partial or Complete Disintegration at 15 sec?	2 min	10 min
	96.3%	71.8%

Figure 3a and b: (a) Mean (+SD) blood concentration-time profiles for (a) buprenorphine and (b) nor-buprenorphine (both figures dose-normalised to 4mg dose to allow analysis of patients on different personal maintenance doses)

(a)



(b)



'bup-lyo' - combination of 15 profiles from 8 subjects
'bup-SL' - combination of 6 profiles from 3 subjects

Table 1: Clinical procedures

Dose induction: Following randomisation, subjects were titrated up to a personalised effective single daily dose of the study medication (either 'bup-lyo' or 'bup-SL'). An effective single daily dose was judged by both patient and clinician to be correct and was assessed through: objective (OOWS) and subjective scoring of severity of opiate withdrawal symptoms (SOWS [25]). VAS scoring of severity of withdrawal, severity of craving, and adequacy of 'hold' from the current prescribed dose.

Titration Period (Study Days 1-7): after subjects had reached their effective dose, they were then observed daily on the same dose for the remainder of this period.

Maintenance Period (Study Days 8-14): throughout this period, the dose of study medication was maintained and not altered unless on overriding clinical grounds.

Extension Period (Study Days 15 to 29): during this later stage, all 'bup-lyo' randomised subjects were switched to standard sub-lingual buprenorphine ('bup-SL') (either directly or tapered over a period of up to 4 days). For all subjects (i.e. regardless of randomised originally to 'bup-lyo' or 'bup-SL'), there was an opportunity for further dose adjustment during the Extension Period.

Table 2: Characteristics of the two randomised groups ('bup-lyo' vs 'bup-SL') (*total population in italics*)

		Lyophilised oral buprenorphine (‘bup-lyo’) (n=23) Mean (SD) Median (range)	Sublingual buprenorphine (‘bup-SL’) (n=13) Mean (SD) Median (range)	<i>Total study population (n=36)</i> Mean (SD) Median (range)
Age (years) (at entry to trial)		42.0 (8.0) 43 (26-58)	42.0 (10.0) 45 (23-53)	<i>42.0 (8.6) 44.5 (23-58)</i>
Age (years) of first opiate use		25.4 (8.7) 22 (11-41)	25.7 (9.4) 23.0 (14-42)	<i>25.5 (8.8) 22.5 (11-42)</i>
Number of years of opiate use		16.6 (11.3) 15 (2-47)	16.3 (10.3) 13 (3-14)	<i>16.5 (10.8) 14 (2-47)</i>
Gender	Male	20	11	31
	Female	3	2	5
Ethnicity	Caucasian	15	8	23
	Asian	0	1	1
	‘Other’	(7)	(4)	(11)
	of which:			
	‘Black British’	2	4	6
	‘African/Caribbea	1	0	1
	n’ ‘African/British’	1	0	1
	‘Mixed	1	0	1
	Black/white’	1	0	1
	‘White African’	1	0	1
OST at time of entering trial	None	2	0	2
	Buprenorphine	15	10	25
	Methadone	6	3	9
Using illicit opiates pre- trial	Yes	13	10	23
	No	9	3	12
	Not known	1	0	1
Injecting history	Never	12	6	18
	<u>Past</u>	10	5	15
	Current	0	2	2
	Unknown/refused	1	0	1
Hep C Status	Positive	3	6	9
	Negative	16	7	23
	Cleared	4	0	4

Table 3 - Assessments of respiratory function with continuous oximetry – ‘bup-lyo’ vs ‘bup-SL’

	Cumulative Total SpO2<90% 0-30 min post-dose		Incidence of SpO2<90% for =>1min, 0-30 min post-dose		Cumulative Total SpO2<90% 0-120 min post-dose		Incidence of SpO2<90% for =>1min, 0-120 min post-dose	
	‘bup-lyo’ Mean (SD)	‘bup-SL’ Mean (SD)	‘bup-lyo’ Mean (SD)	‘bup-SL’ Mean (SD)	‘bup-lyo’ Mean (SD)	‘bup-SL’ Mean (SD)	‘bup-lyo’ Mean (SD)	‘bup-SL’ Mean (SD)
Titration Day 1	8.1 (16.69)	158.3 (510.09)	0 (0)	0.3 (1.15)	68.1 (88.40)	207.5 (123.74)	0 (0)	0.5 (0.71)
Titration Day 1.1	22.9 (42.37)	157.8 (402.49)	0.1 (0.27)	0.7 (2.00)	67.3 (65.91)	958.0 (1969.18)	0.2 (0.38)	3.8 (8.5)
Maintenance Day 2	6.1 (11.95)	177.0 (544.00)	0 (0)	0.1 (0.32)	68.0 (92.37)	499.3 (959.26)	0.2 (0.49)	0.9 (1.46)
Maintenance Day 7	7.1 (13.47)	14.0 (31.25)	0 (0)	0 (0)	61.1 (88.94)	226.0 (281.46)	0 (0.5)	0 (1.27)

Web-appendix Table A1: Inclusion and exclusion criteria for the trial

Inclusion Criteria:

Each subject had to meet the following criteria to be eligible:

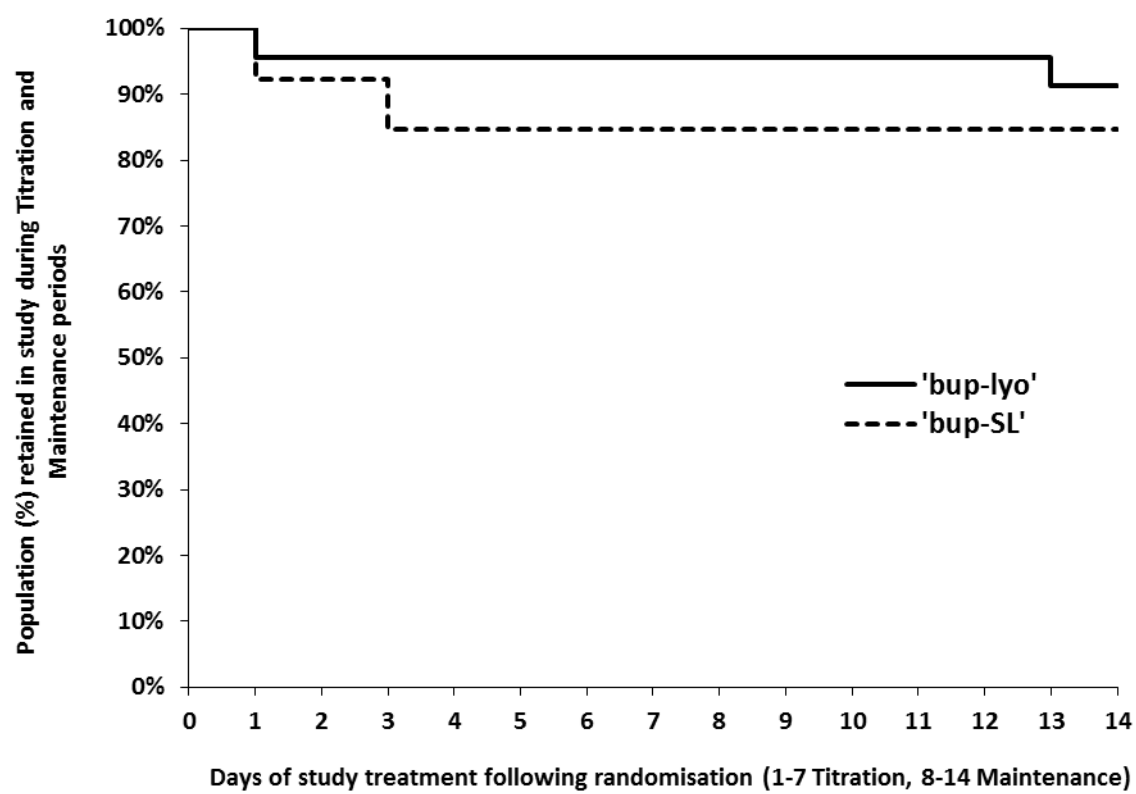
1. Opioid-dependent subjects, suitable for opiate maintenance treatment;
2. Aged ≥ 18 to ≤ 60 years;
4. Body Mass Index (BMI) of ≥ 18.0 and ≤ 30.0 kg/m²;
5. Capable of providing voluntary informed consent;
6. For female subjects of child-bearing potential an adequate form of contraception had to be adhered to for at least 30 days prior to study entry (or evidence of two negative pregnancy tests at least 7 days apart before first dose of study drug). The subject had to agree to adhere to a contraceptive regimen continuously until 30 days after the last Extension Period Visit
7. A non-custodial stable residence and telephone number
8. For subjects enrolling in the PK part of the study, venous access had to be suitable for the collection of serial blood samples. All other subjects had to have venous access adequate for the collection of blood for baseline measures.
9. No treatment with either buprenorphine or methadone within one day of the scheduled commencement of study treatment. If potential study subjects did not meet this criterion subjects could enter a Pre-Randomisation Management Period, during which buprenorphine and methadone were to be excluded for at least one day. Where necessary, interim treatment with oral morphine (either as slow-release or immediate-release oral morphine) could be provided;
10. The Screening electrocardiogram (ECG) was to be normal or have no clinically significant abnormalities.

Exclusion Criteria:

Subjects who met any of the following criteria were excluded from the study:

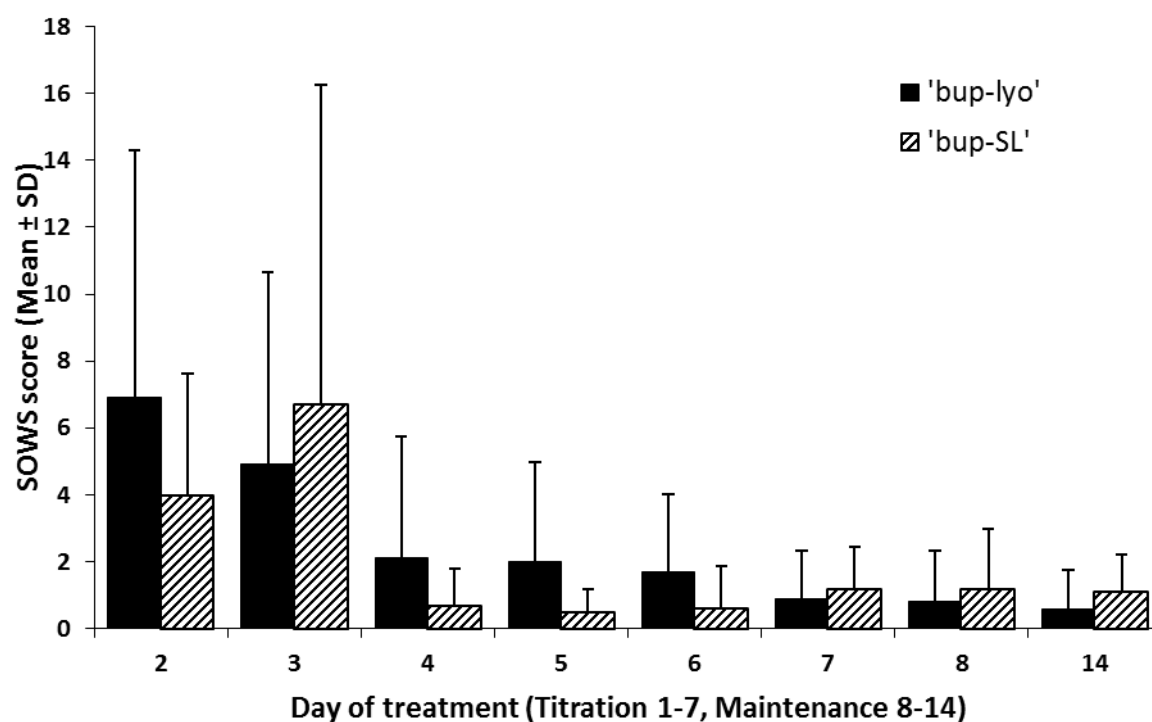
1. Hypersensitivity to buprenorphine or any other component of the oral lyophilisate;
2. Dependent use of cocaine or amphetamines requiring specific treatment;
3. Continued daily use of other opioids (i.e. non-prescribed) from 24 hours prior to the first dose of buprenorphine until the end of the study, in a manner which, in the opinion of the Investigator, compromised subject safety or interfered with the valid contribution to the study data;
4. Severe hepatic insufficiency (defined as liver function tests, including alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase, greater than 3 times the upper limit of normal);
5. Subjects suffering from severe respiratory insufficiency;
6. Subjects suffering from acute alcoholism or delirium tremens;
7. Dependent use of benzodiazepines, which could have potentiated respiratory depression, above recommended therapeutic doses or subjects who were taking benzodiazepines in a manner which, in the opinion of the Investigator, compromised subject safety;
8. Concomitant medication known to interact with buprenorphine;
9. Administration of any approved or investigational long-acting injections of antipsychotic medications;
10. Current psychiatric diagnosis of major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would have compromised the subject's ability to complete the study;
11. Female subjects who had a positive pregnancy test, mothers who were lactating, women who refused to agree to adequate contraception and pregnancy tests during the study, or women who were planning to become pregnant during the period of the study;
12. Participation in a clinical study of a pharmacological agent within the six months prior to Screening;
13. Any other factor that in the opinion of the Investigator would have made the subject unsafe or unsuitable for the study.

Web-appendix Figure A1: Retention of subjects during randomised treatment

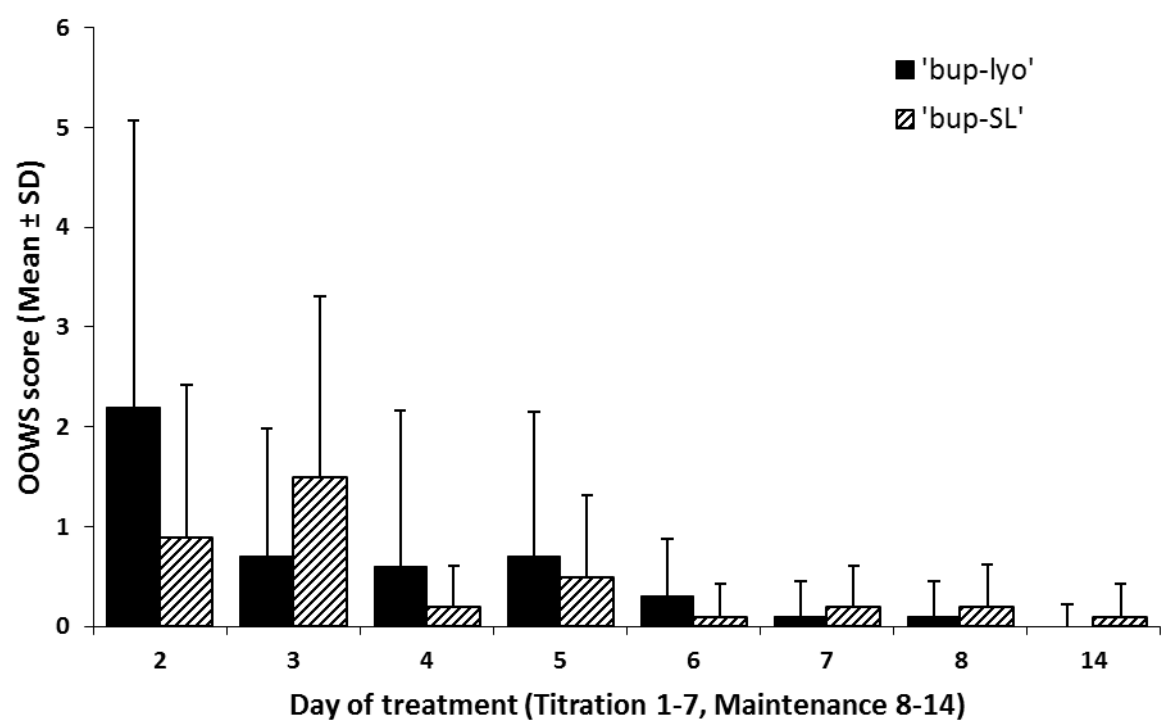


Web-appendix Figure A2a&b: SOWS and OOWS scores during randomised treatment

(a) SOWS:

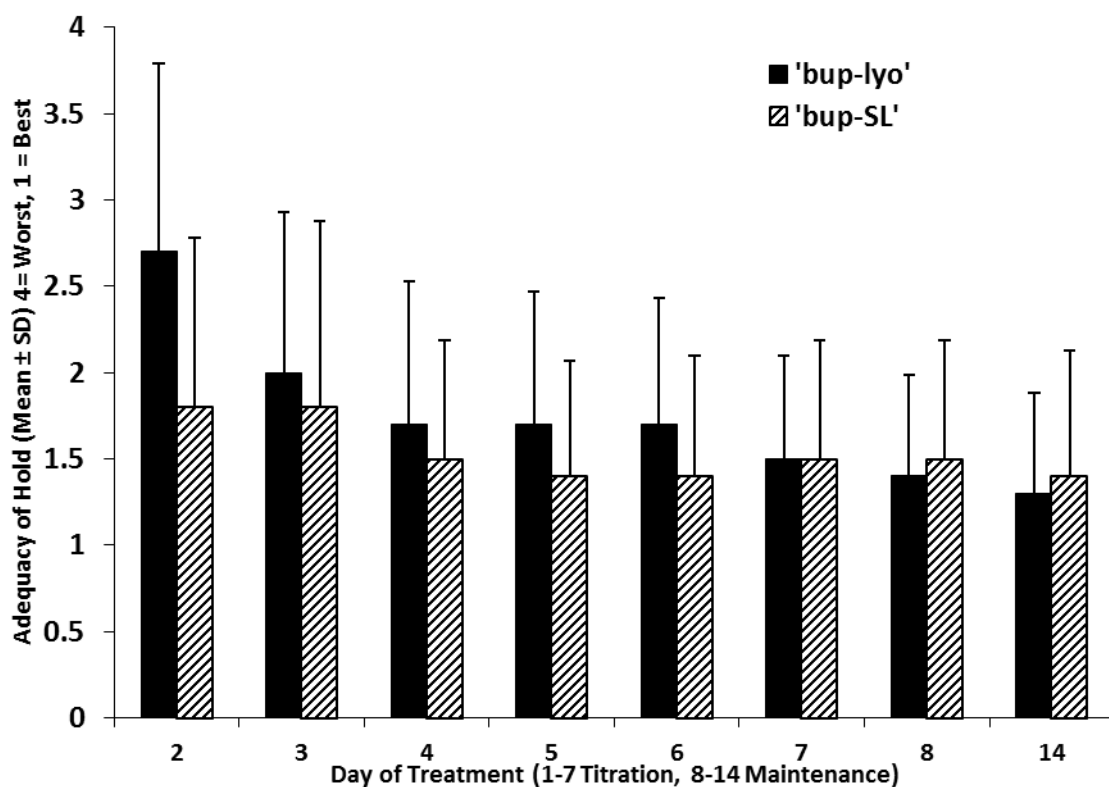


(b) OOWS:

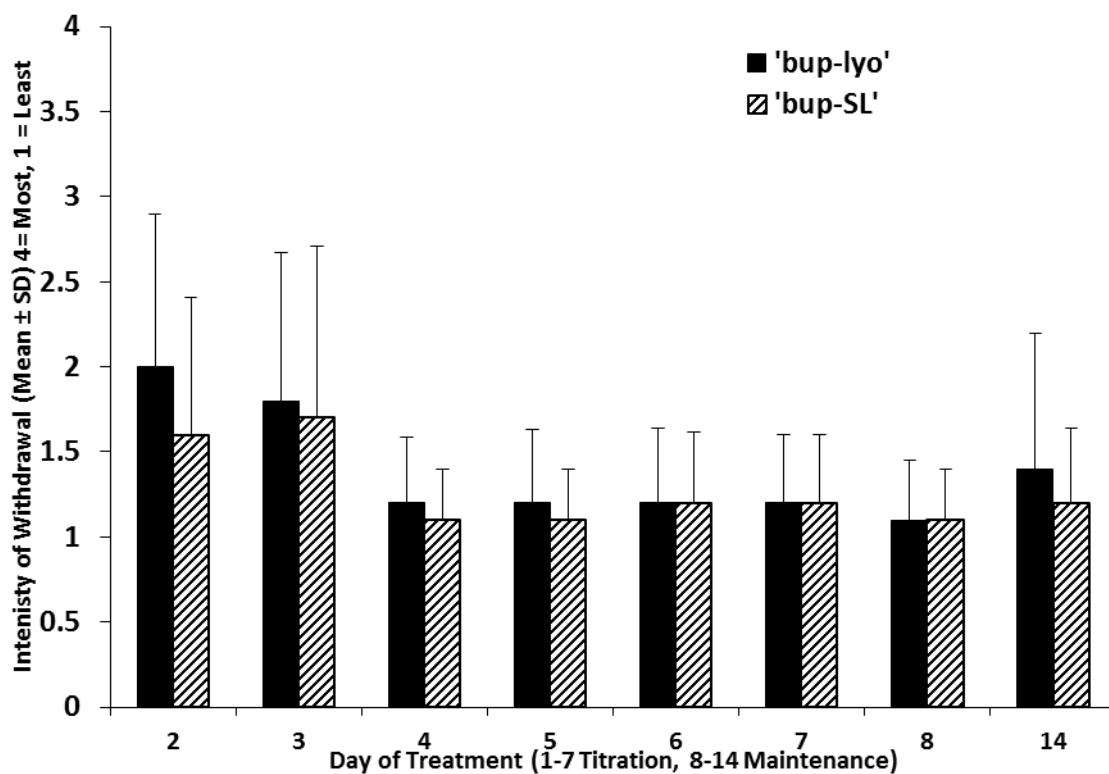


Web-appendix Figure A3a,b,c: Adequacy of 'Hold', intensity of 'Withdrawal', intensity of 'Craving' during randomised treatment

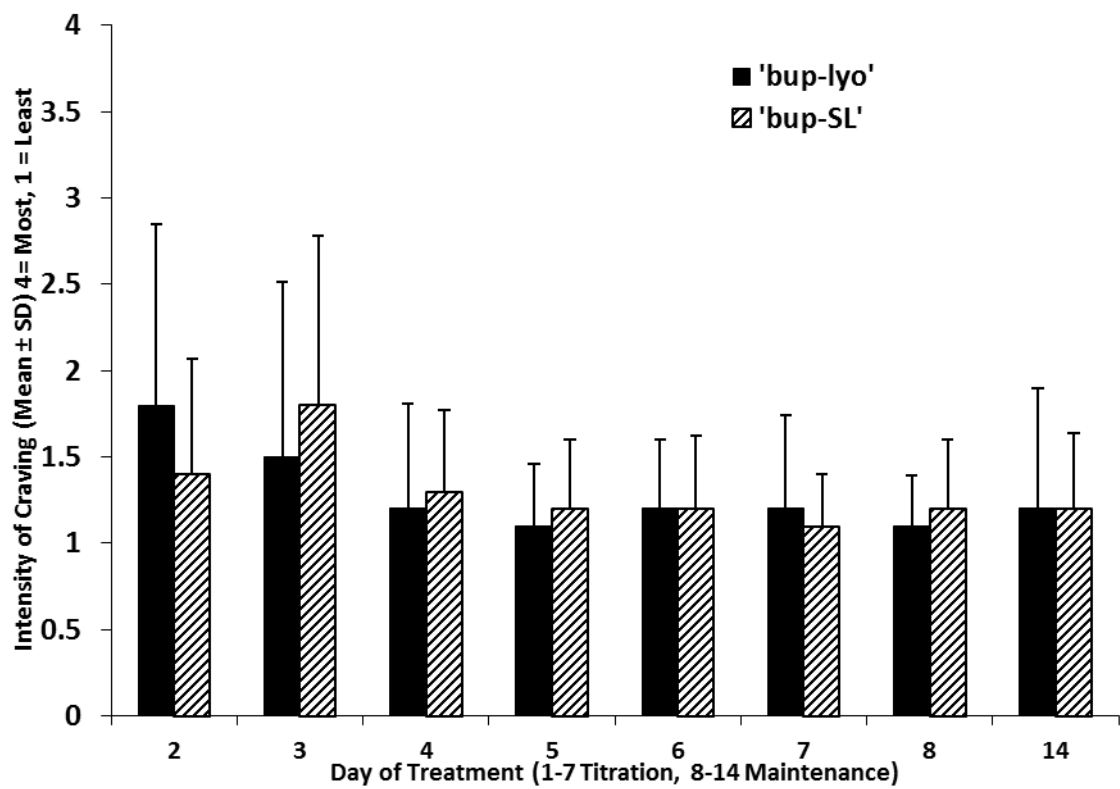
(a) Adequacy of 'Hold':



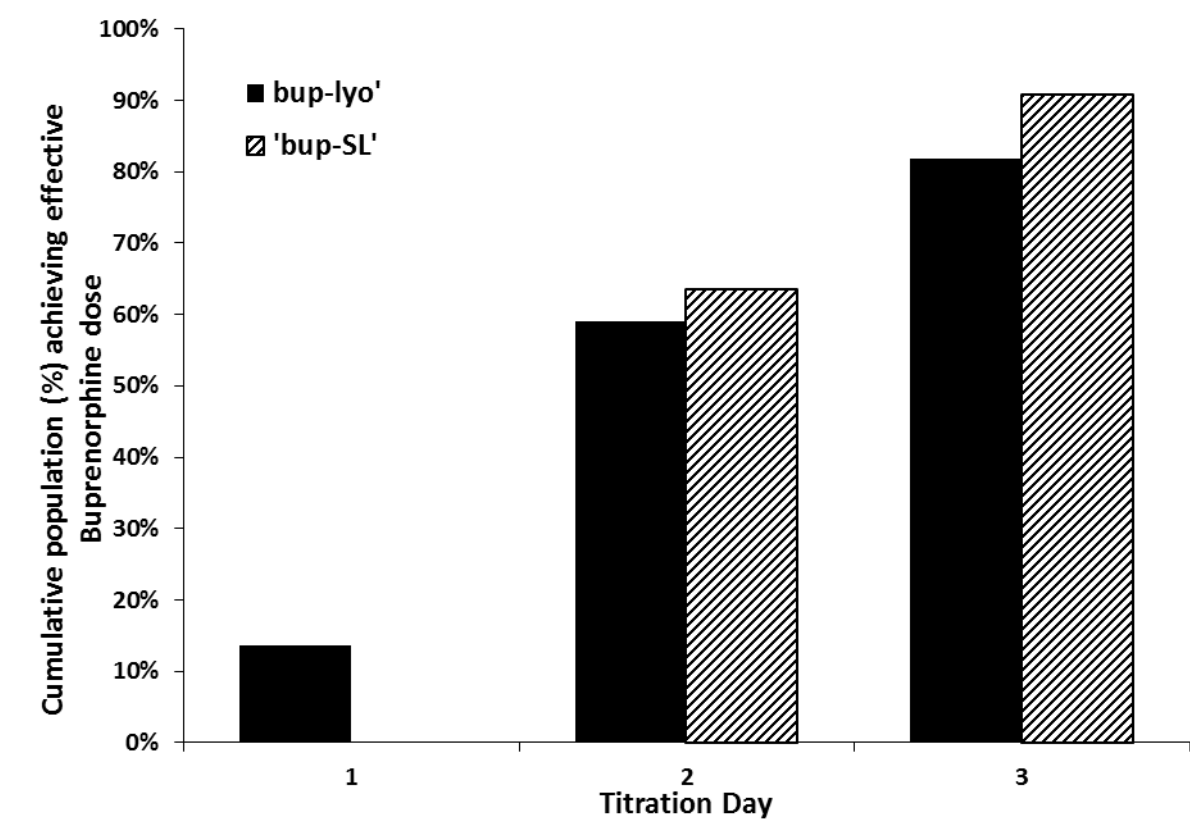
(b) Intensity of 'Withdrawal':



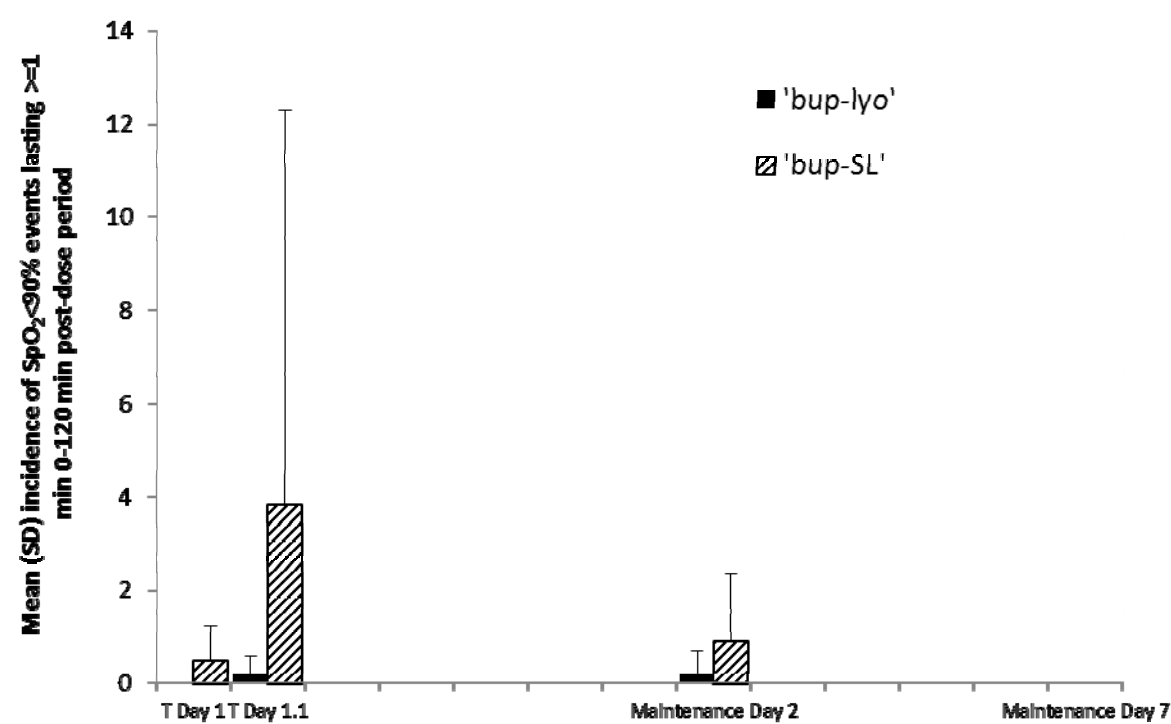
(c) Intensity of 'Craving':



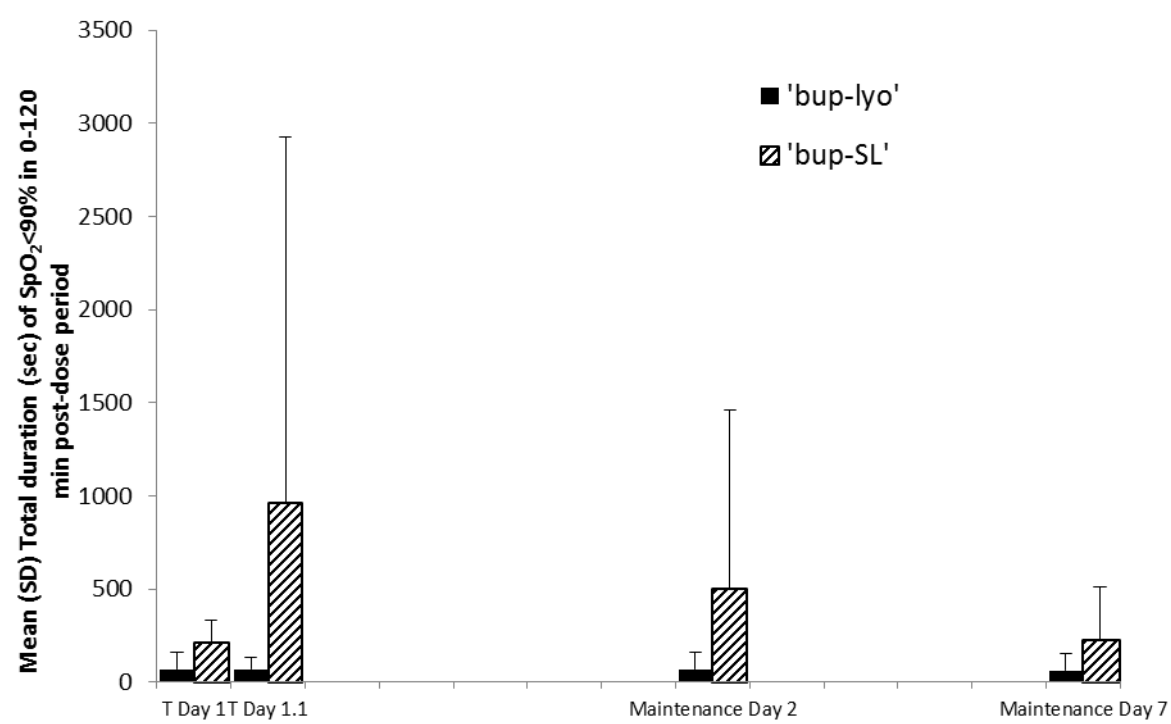
Web-Appendix Figure A4: Time to achievement of maintenance dose during Titration period



Web-Appendix Figure A5a: Mean incidence of SpO₂<90% (sec) ≥1min 0-120 min post-dose



Web-Appendix Figure A5b: Mean Total Duration (SD) of SpO₂<90% (sec), 0-120min post-dose



Web-Appendix Table A2: Deaths, Serious Adverse Events (SAEs), Adverse Events (AEs) and Treatment-Emergent Adverse Events (TEAEs)

Treatment-Emergent Adverse Events (TEAEs) (n=36)

	'bup-lyo'		'bup-SL'		Extension ('bup-SL')	
	N=23		N=13		N=32	
	n	(%)	n	(%)	n	(%)
Number of subjects with Serious Adverse Events (SAEs)	0		0		0	
Adverse Events (AEs) and severity						
Severe	0		0		0	
Moderate	4	(17.4)	3	(23.1)	5	(15.6)
Mild	13	(56.5)	1	(7.7)	8	(25.0)
Number of subjects with TEAEs resulting in withdrawal from the study	0		0		0	
Number of Deaths	0		0		0	